EBUS FNA cytology

The Swansea Experience
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Endobronchial ultrasound FNA cytology

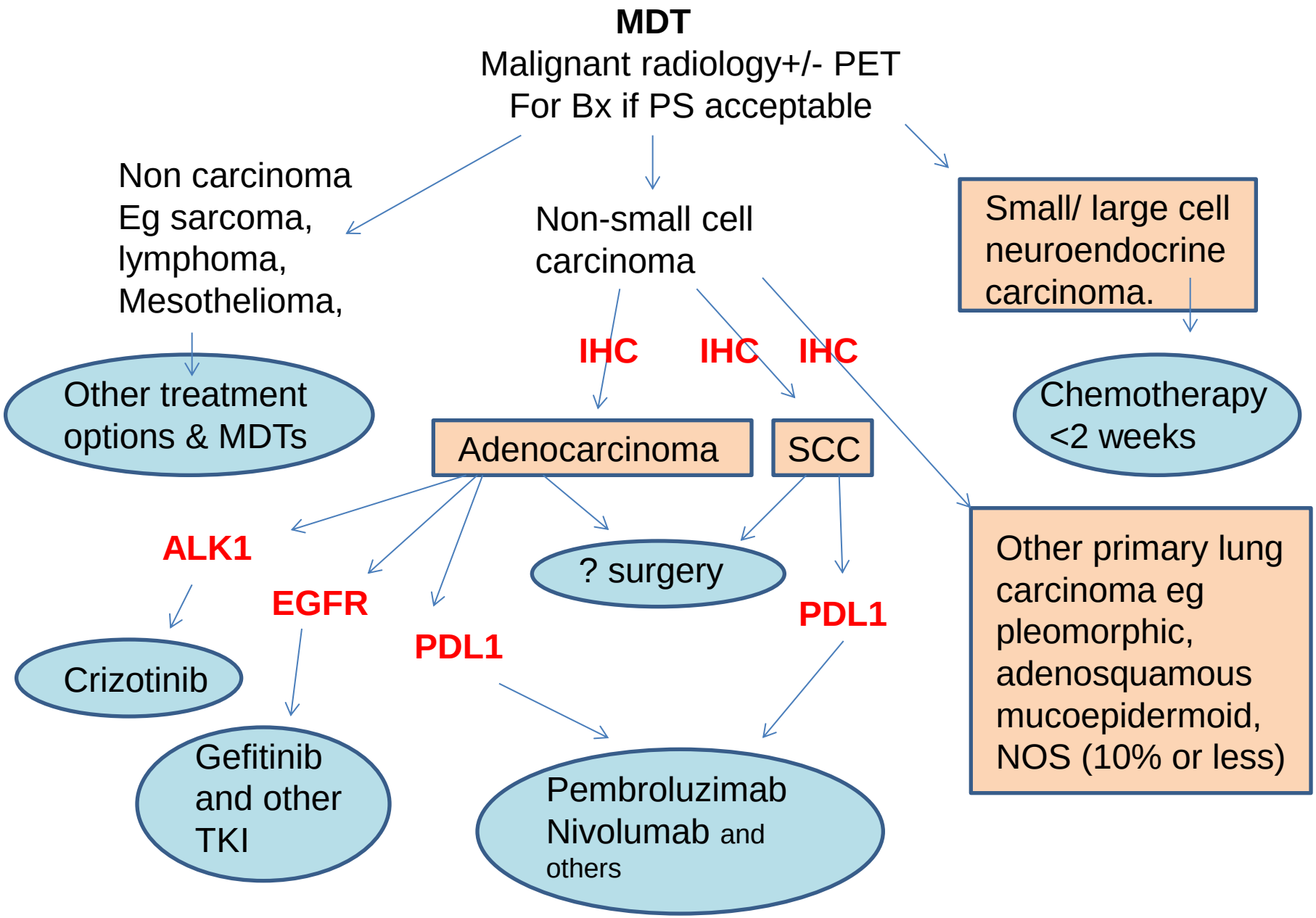
- What are they?
- Why do we need them?
- How do we process them?
- Does it work for patients, physicians, oncologists, and pathologists?

EBUS what are they?:

- Sampling of tumour and/ or lymph nodes that may be accessible via main bronchi at bronchoscopy.

Why do we need EBUS?

- Accurate primary diagnosis
- Accurate staging
- Plan treatment


MDT
Malignant radiology+/- PET
For Bx if PS acceptable
Non carcinoma
Eg sarcoma,
lymphoma,
Mesothelioma,
Non-small cell
carcinoma
Small/ large cell
neuroendocrine
carcinoma.
Other treatment
options & MDTs
IHC
IHC
IHC
Chemotherapy
<2 weeks
Adenocarcinoma
SCC
ALK1
EGFR
PDL1
? surgery
PDL1
Other primary lung
carcinoma eg
pleomorphic,
adenosquamous
mucoepidermoid,
NOS (10% or less)
Crizotinib
Gefitinib
and other
TKI
Pembroluzimab
Nivolumab and
others

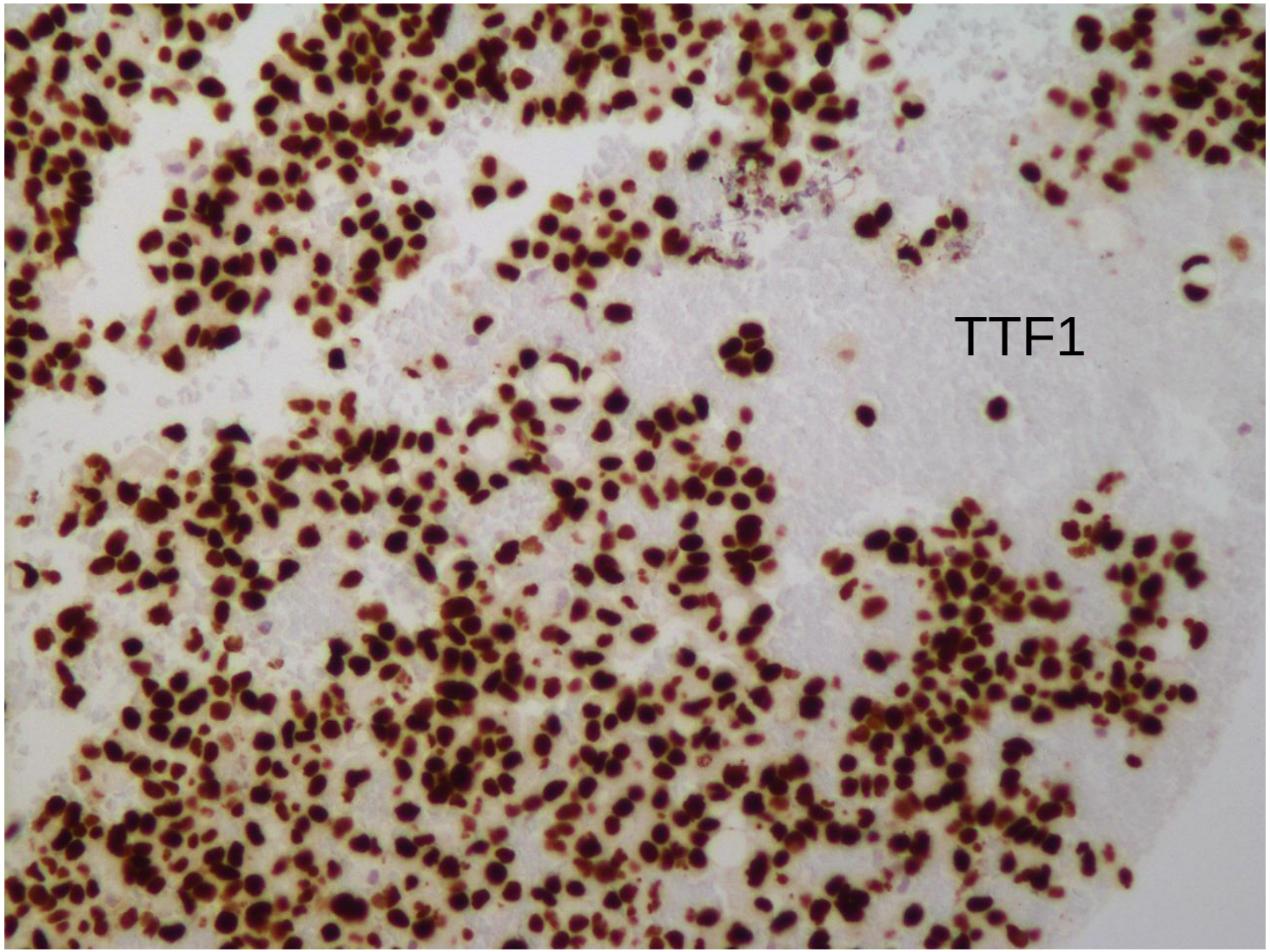
EBUS and diagnostic IHC

- Limited material for an increasing number of tests
- If NSCLC:

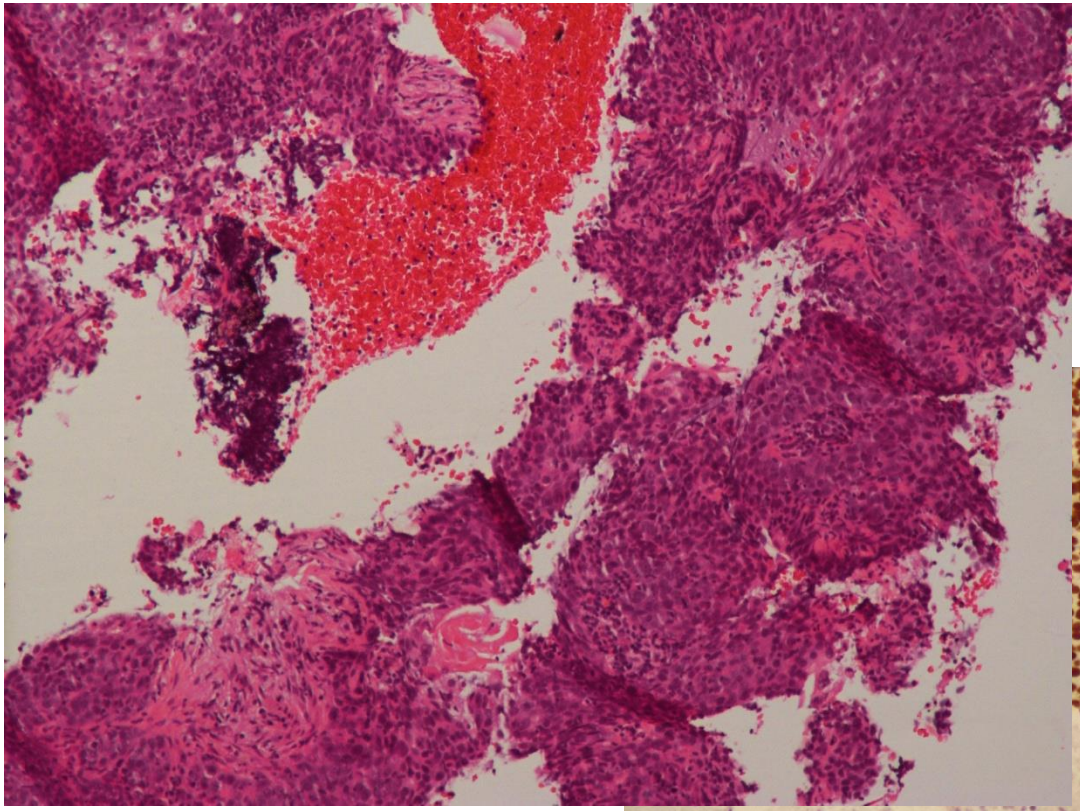
TTF1 and p40 only

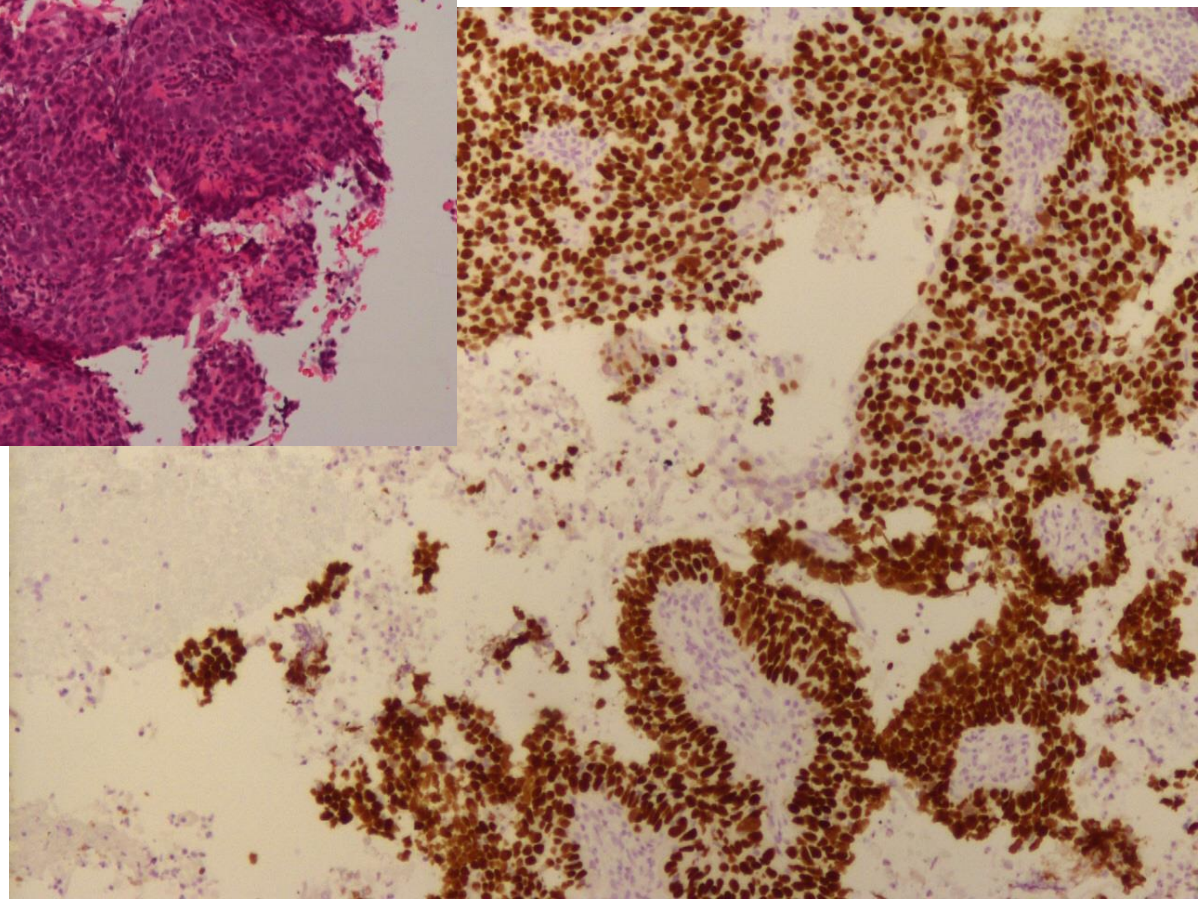
- Know the clinical history
- Napsin A and CK5/6 second round
- Beware p63 and CK7

EBUS and IHC quality

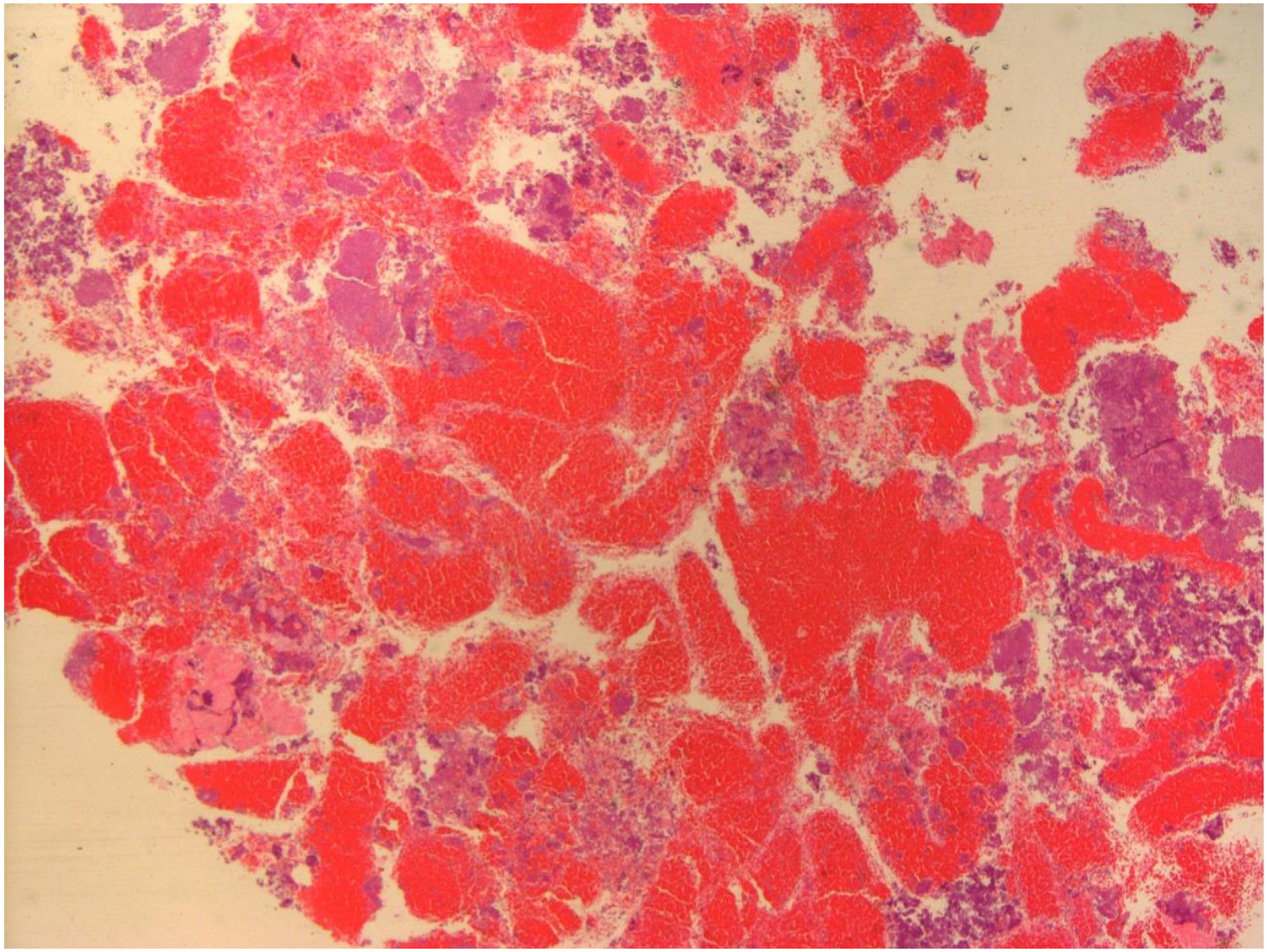


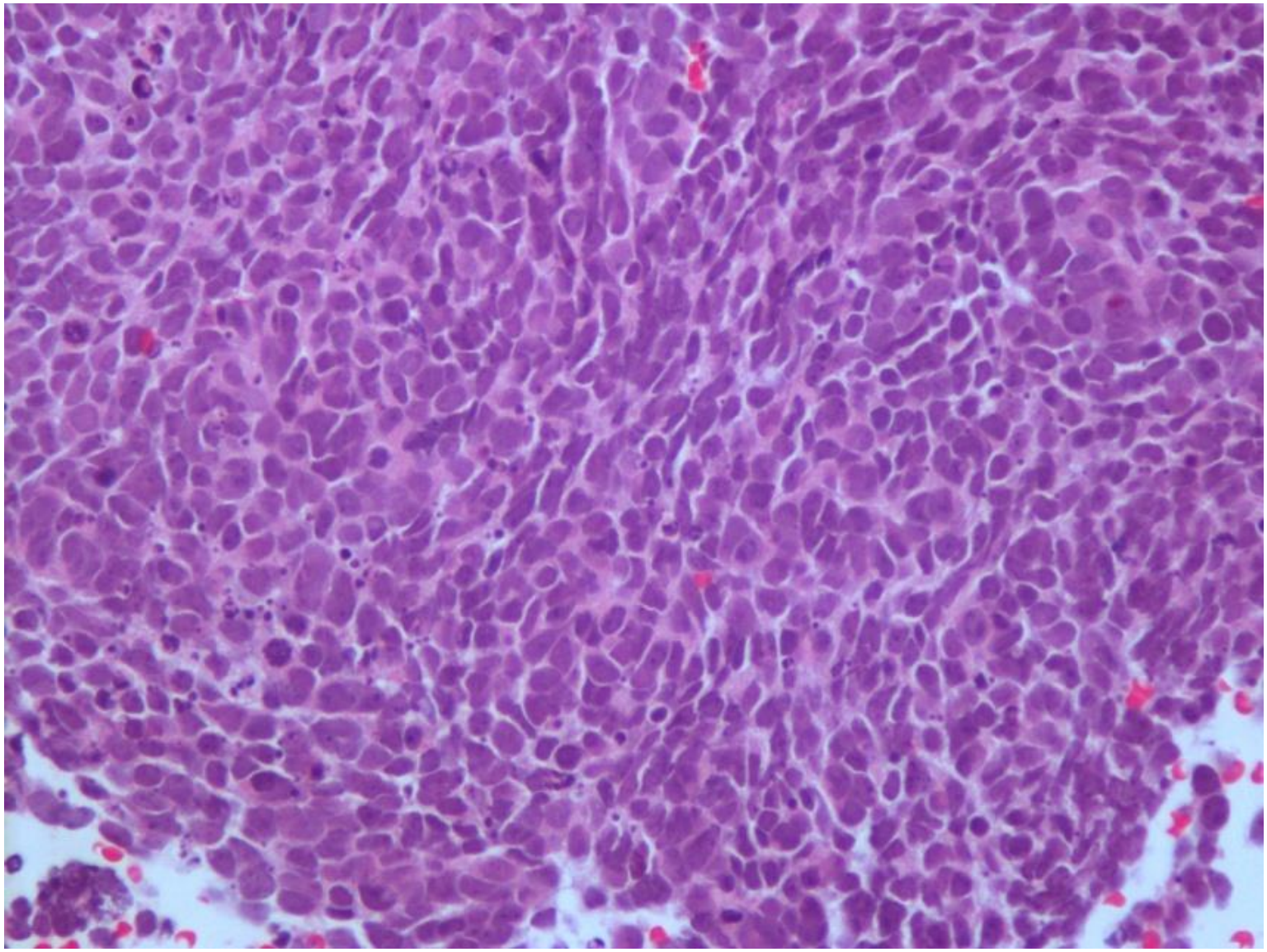
p40

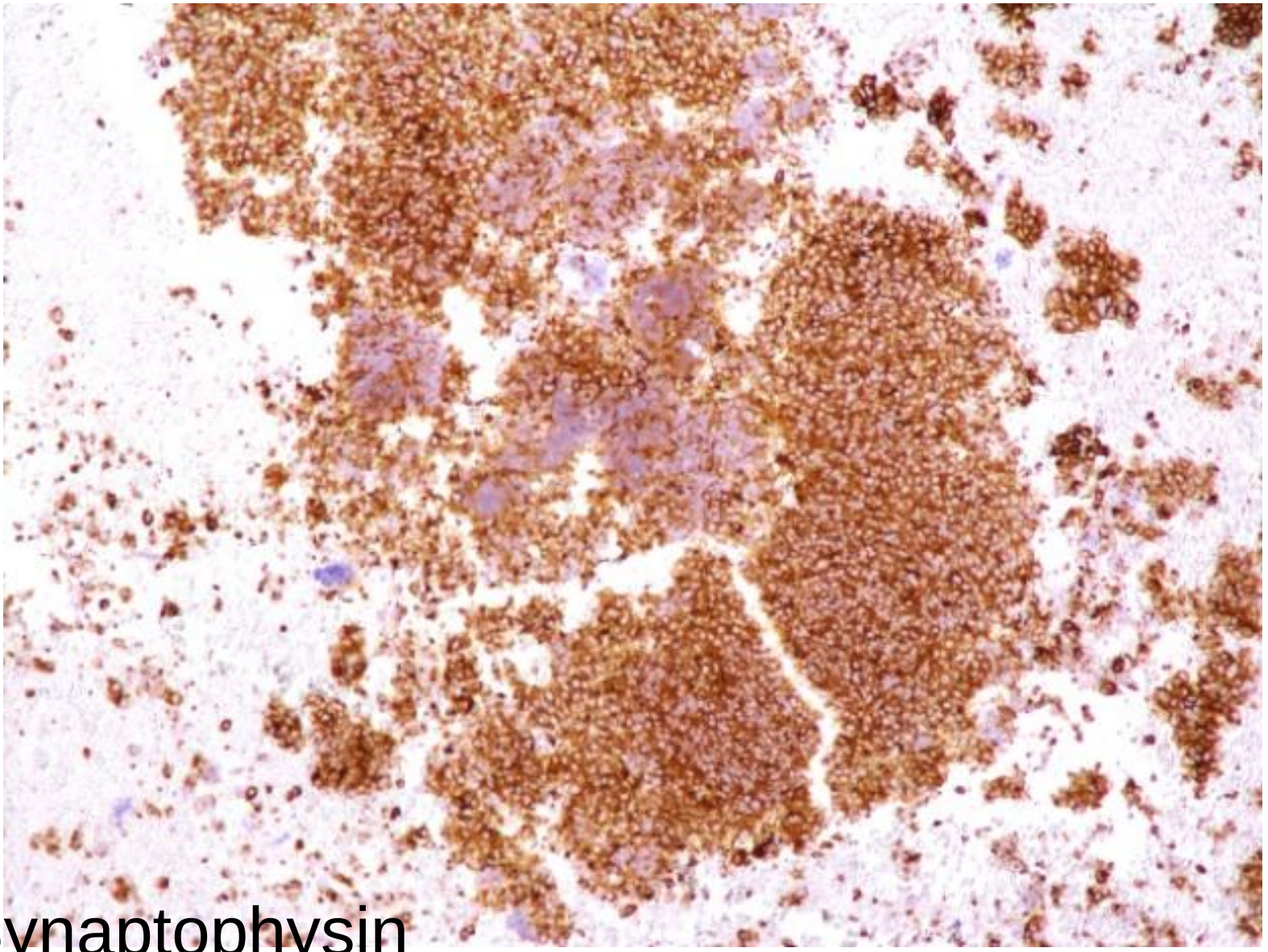




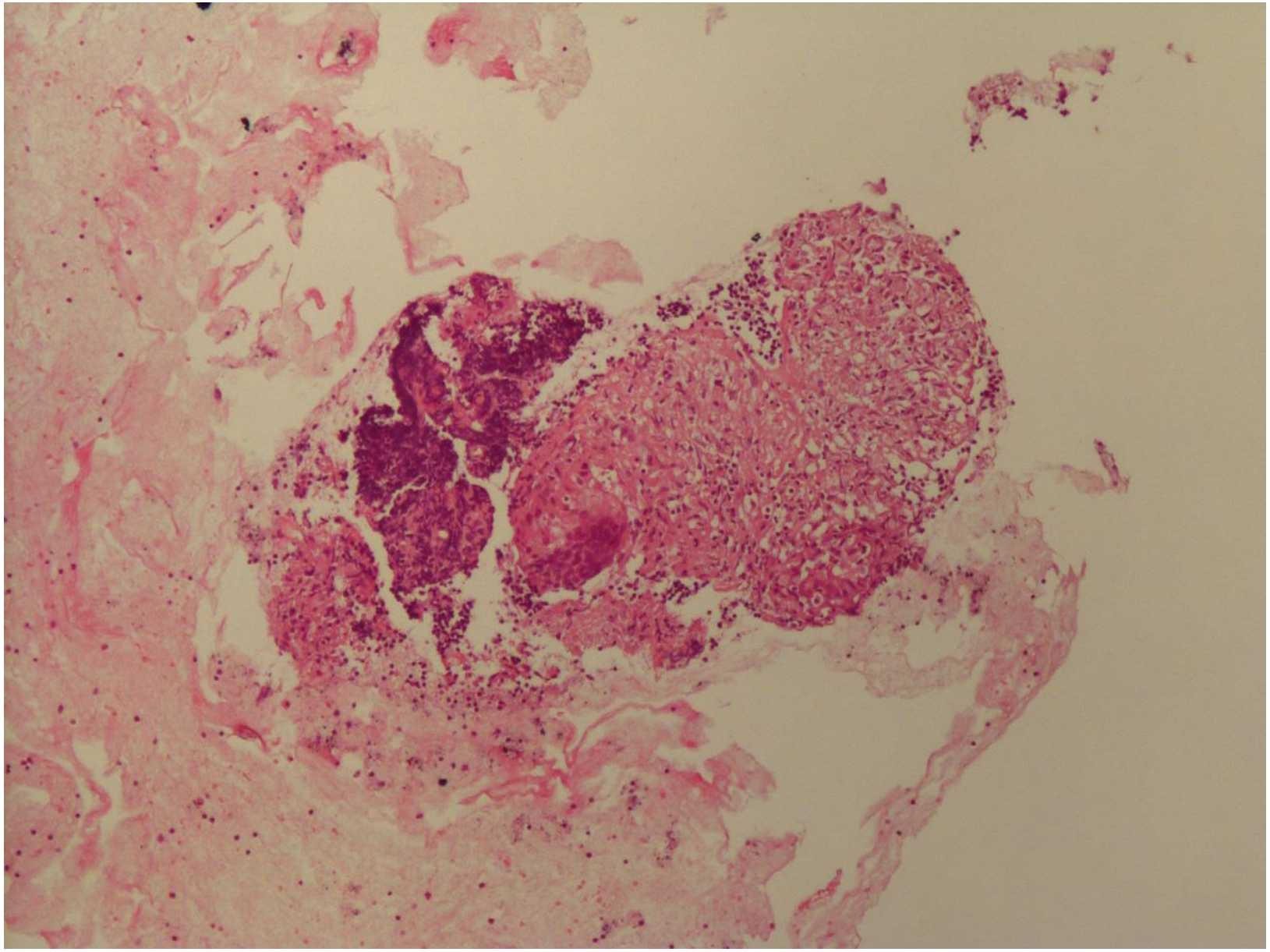
Small cell neuroendocrine carcinoma







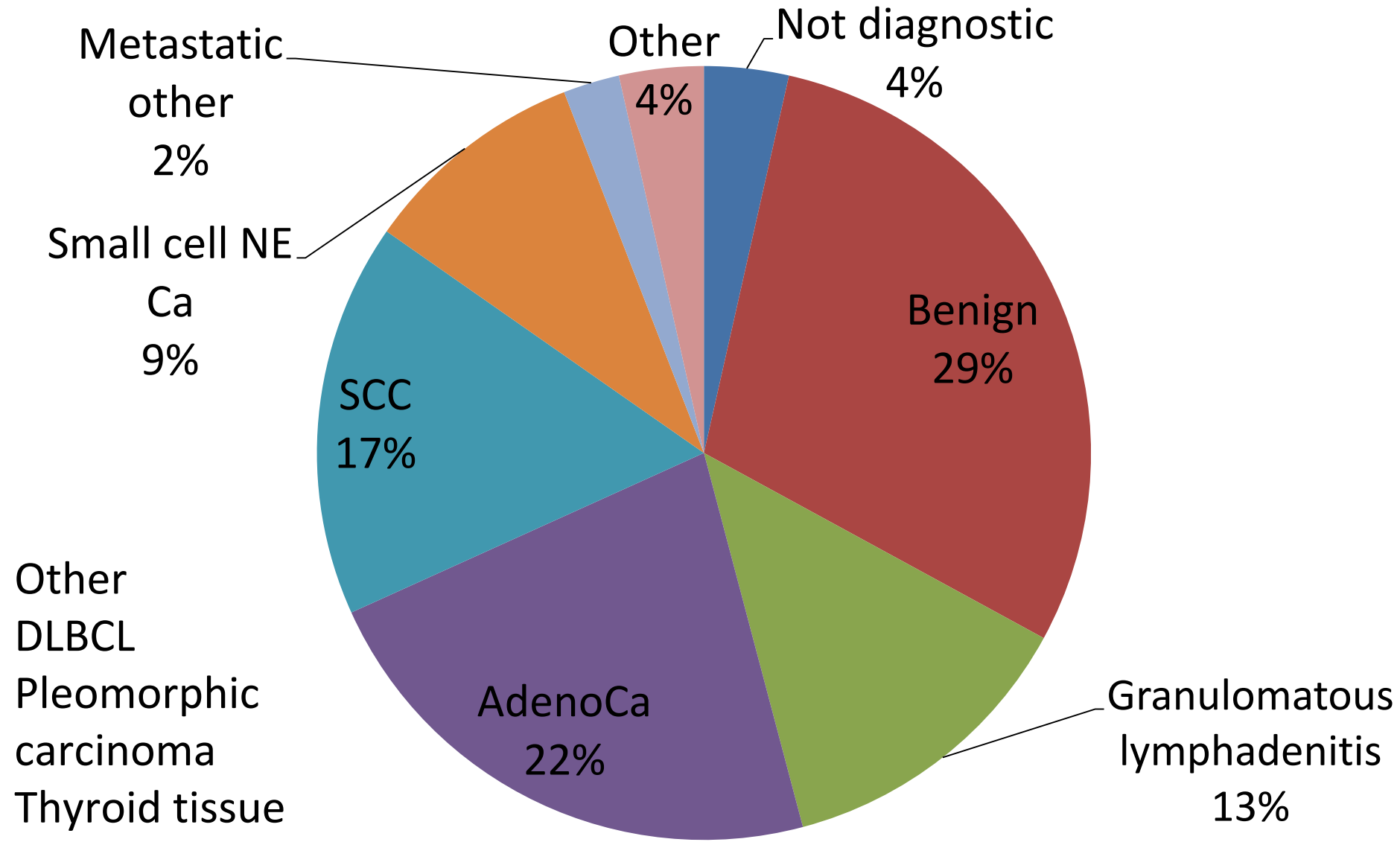
Synaptophysin



Does it work?

- YES
- Diagnostic yield 96%
- 3/84 inadequate in 1 year (too few cells)

ABM EBUS 2017: 84 cases



Literature

- NICE diagnostic yield 79%
- Diagnostic yield 87% Kennedy *et al* Bronchol 2010
- US study 94% (Bhatti HA *et al* J Bronchol Intervent Pulmonol 2013)
- Leicester 88% (Gupta A et al Thorax 2017)

Diagnostic outcomes

Gupta *et al* , Thorax 2017

- Leicester 1083 patients
- Malignant 44%
- Granulomatous 20%
- Benign 24%
- Not diagnostic 12%

NZ, Shaffuddin et al 2014

Asia Pacific Lung Cancer Conference

- SCC 14%
- Adenocarcinoma 19%
- NSCLC NOS 10% (10% WHO upper limit for NOS)
- Small cell 14%
- Malignant other 14%
- Sarcoid 14%
- TB 1%
- Reactive 10%
- Bronchogenic cyst 2%

Ancillary tests in Adenocarcinoma

- Somatic tumour DNA genomic analysis by NGS PCR for EGFR receptor mutation.
- Serum cDNA fragments for EFGR
- ALK1: FISH or immunohistochemistry
- ROS1 immunohistochemistry (<50yr, never smokers) translocation rate around 1%
- PDL1

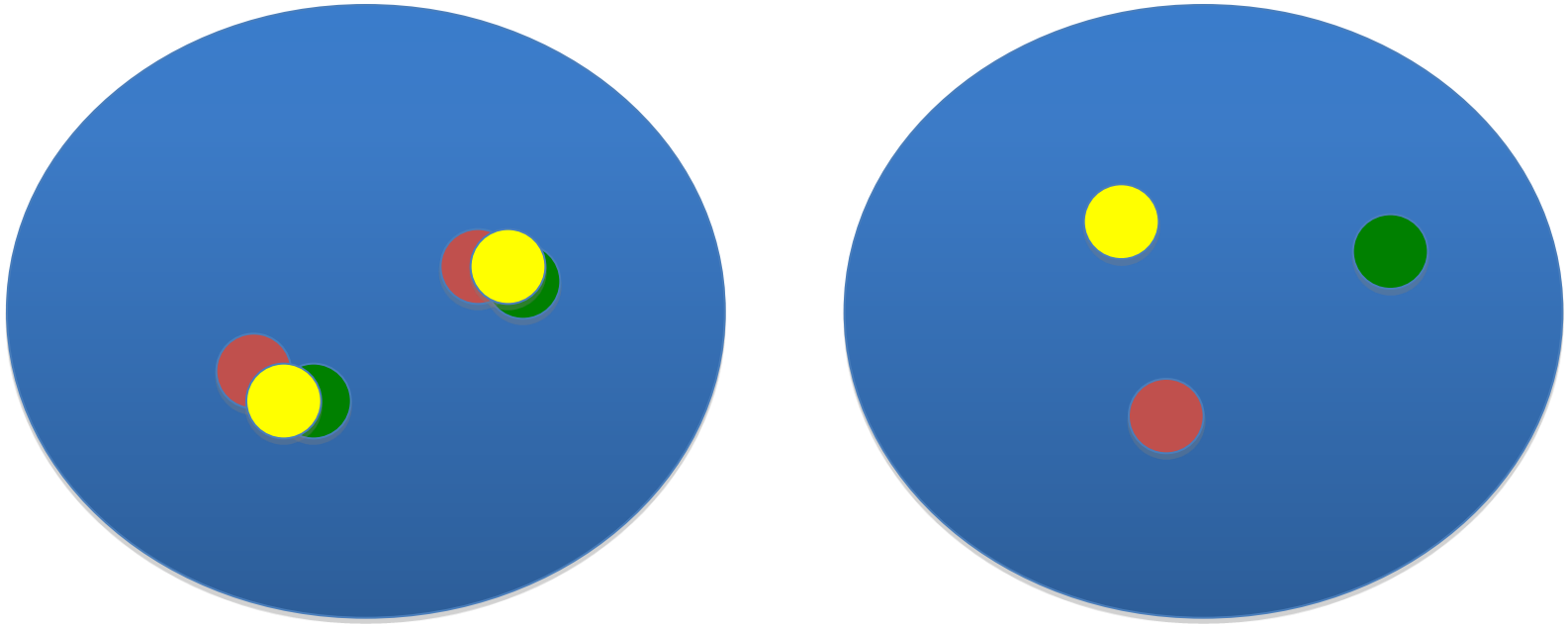
ABM EBUS Adenocarcinoma: EGFR

- 1 EGFR mutation in 13 requests (expect 1/6)
- c.2573 T>G p.Leu858Arg activating mutation
- =L858R mutation in exon 21
- Common, 43% of all mutations

ABM EBUS Adenocarcinoma ALK1

- 8/9 negative for translocation by FISH
- 1/9 test fail due to insufficient DNA
- Unknown quality vs quantity

ALK1: Break apart probe
EML4-ALK fusion
inversion short arm chr 2



Normal

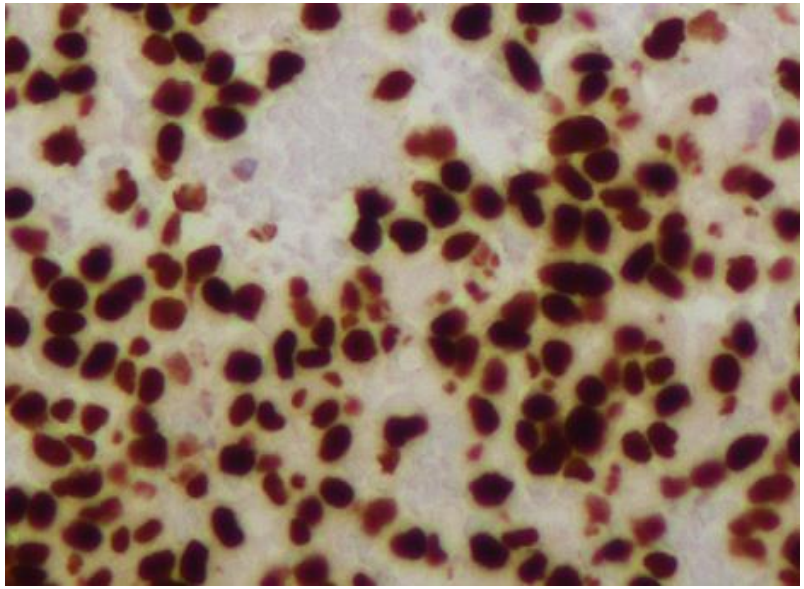
Translocation

ALK1 IHC: DF53 clone

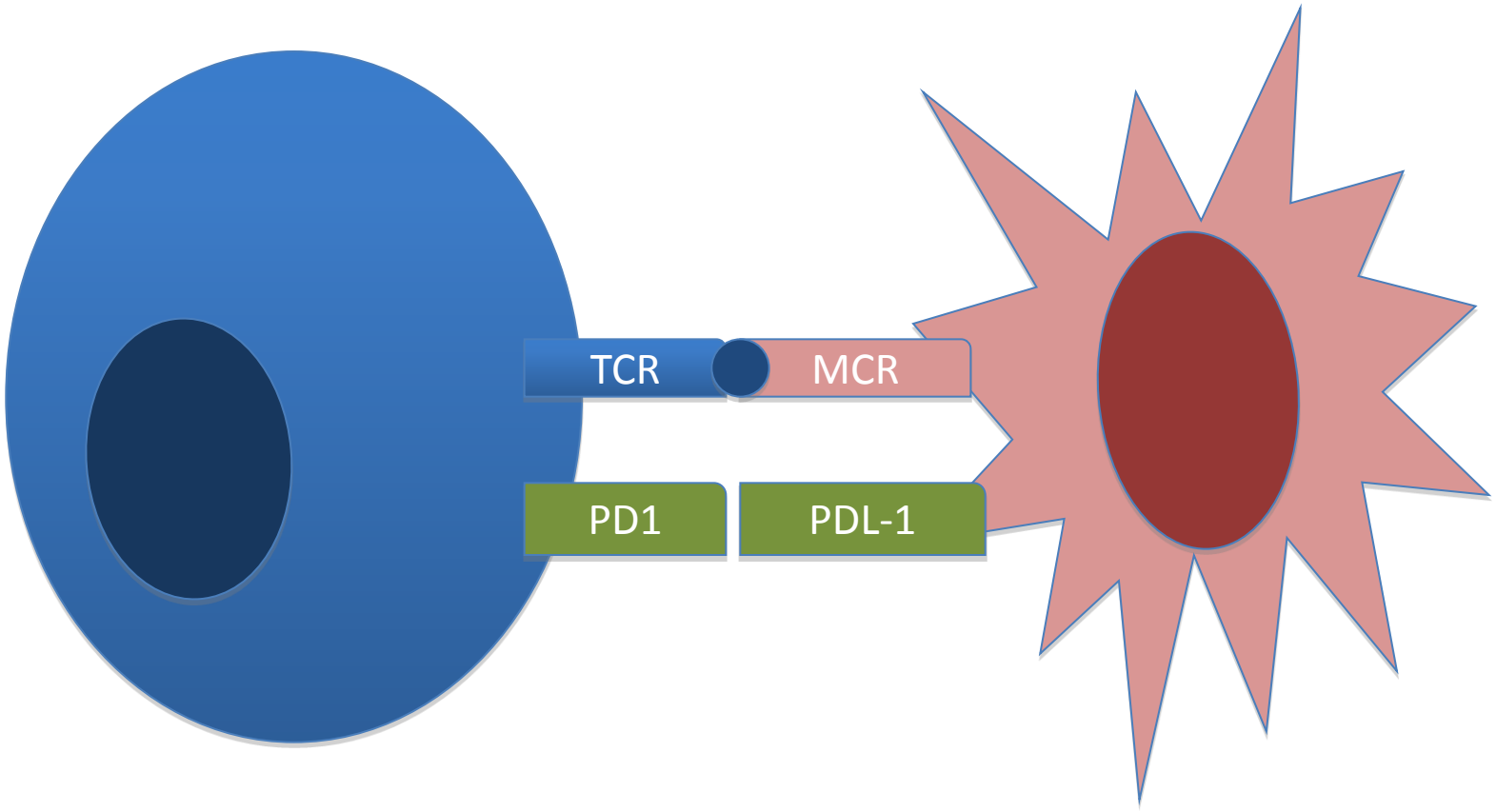
Translocation frequency around 5%

Companion diagnostic

Same accuracy as FISH



T-cell inhibition via PDL-1



PDL-1

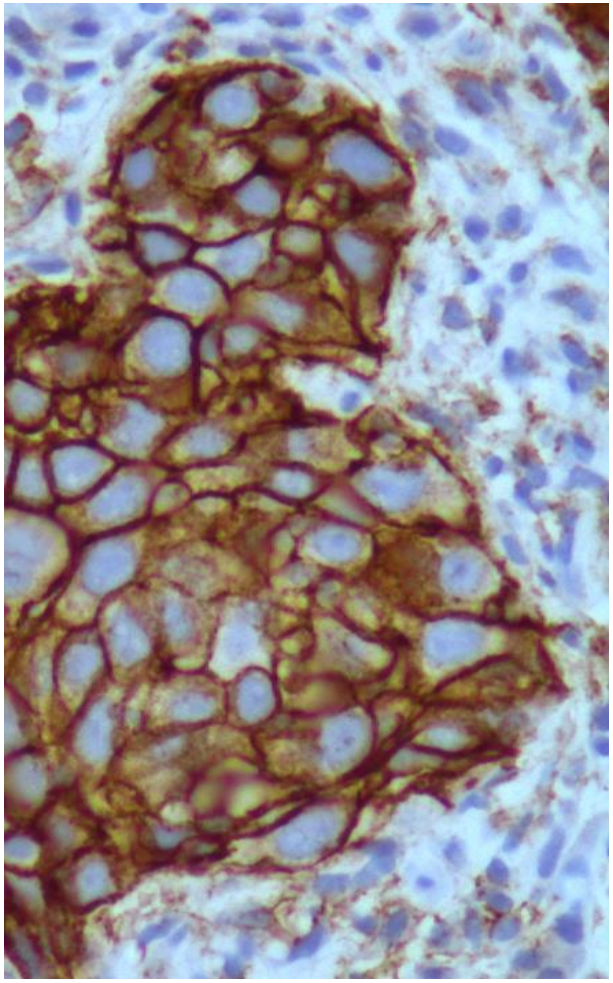
- Diagnosis of adenocarcinoma or squamous carcinoma of lung origin.
- Keynote study, NEJM 2016: Clinical response to Pembroluzimab positively correlates with % staining
- Formalin fixed tissue 6-72 hours.

Reporting thresholds for treatment

- First line >50%
- Disseminated disease >1%
- Beware tumour hetrogeneity

PDL1 stain

- Membrane staining
- Blueprint study JTO 2017
- 4 clones
  - 22C3
  - SP263
  - 28-8
  - SP142
- Report % staining
- Macrophages
- Pathologist training



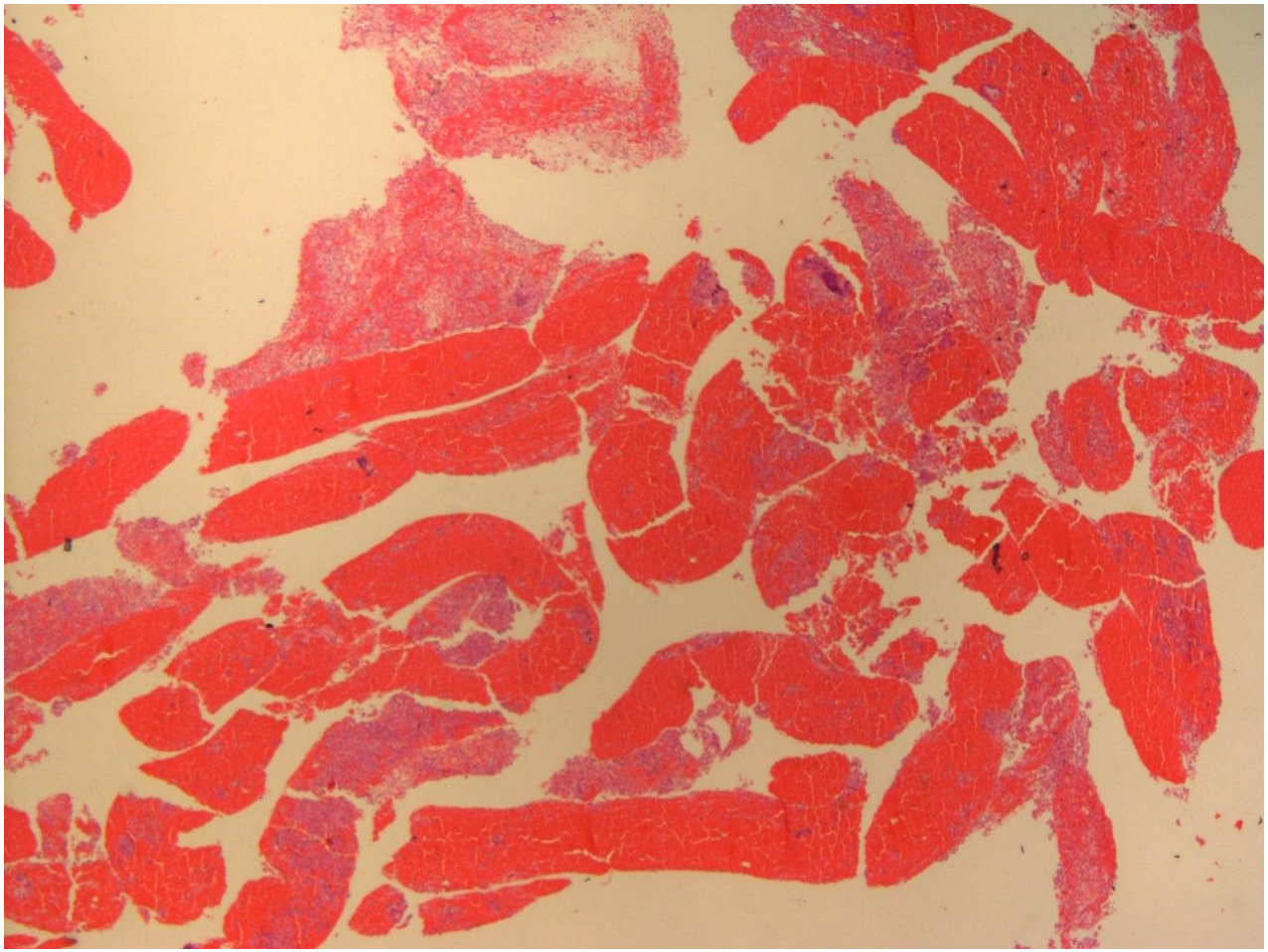
Pre-analytic considerations

- Formalin fixation 6-72 hours

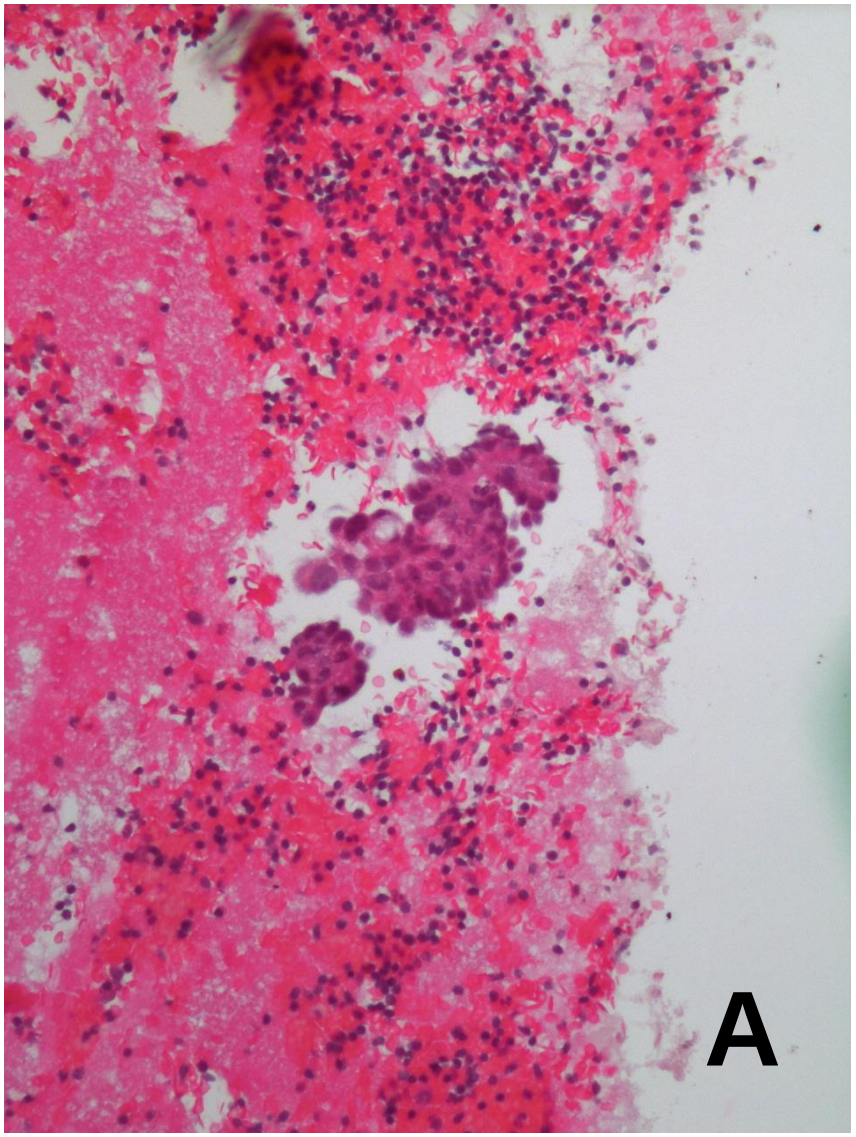
Skov et al Appl Immunohistochem Mol Morphol 2017

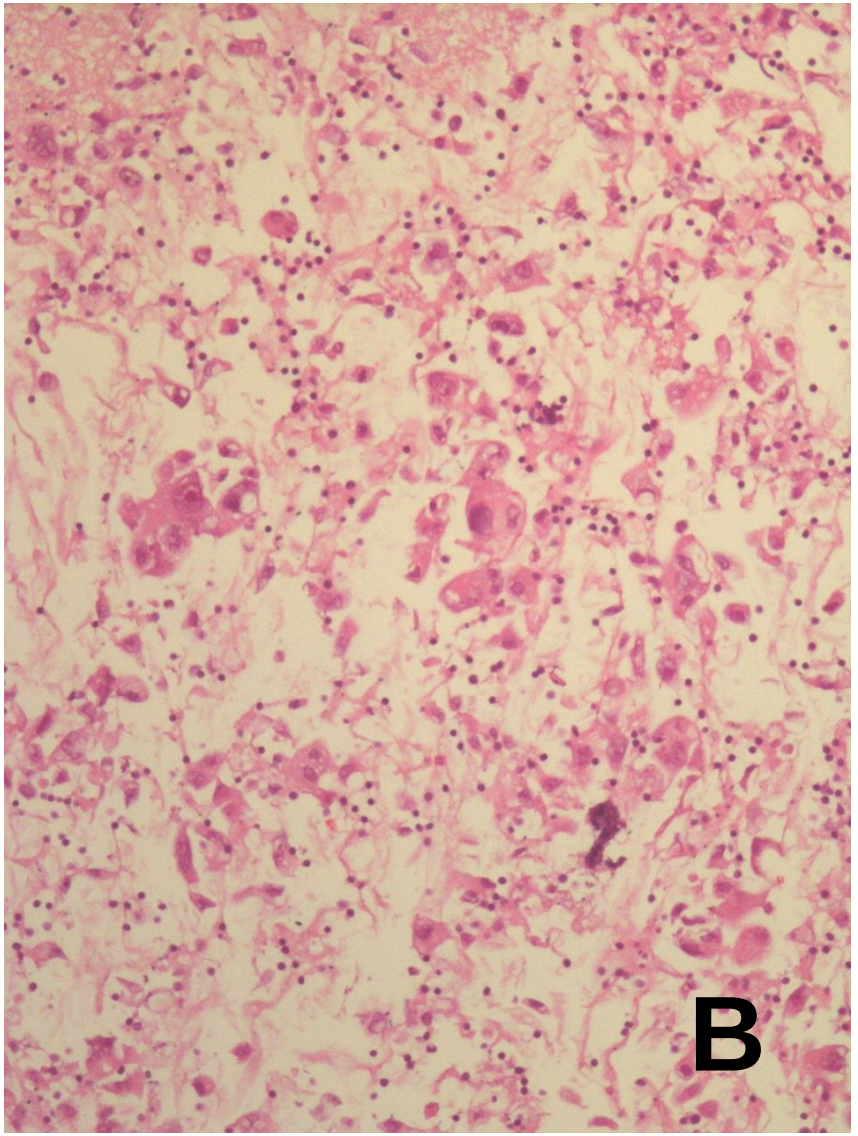
- 86 patients with paired cytology histology samples.
- Cytology material in saline – cell block fixed formalin 18 hours
- 17/86 insufficient cellularity (20%)
- High concordance histology vs cytology
- Conclude EBUS suitable for PDL-1

EBUS in formalin



Spot the difference





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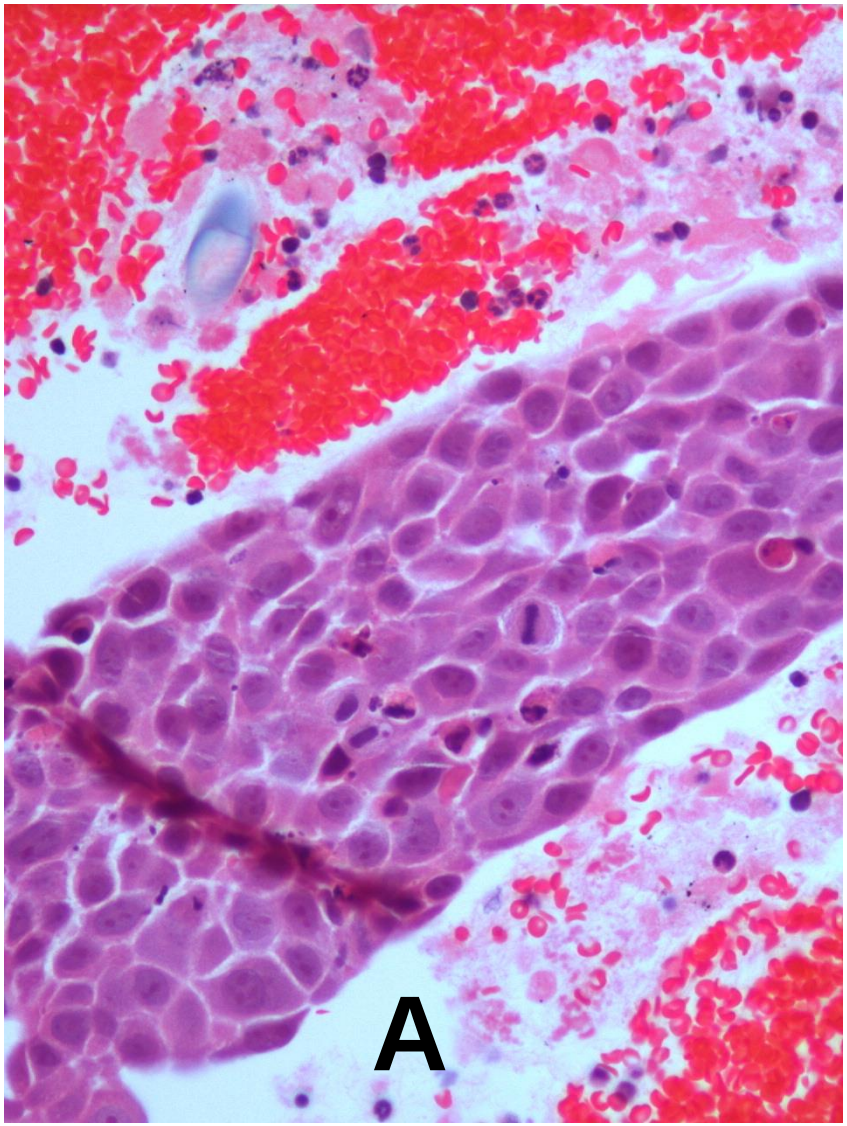
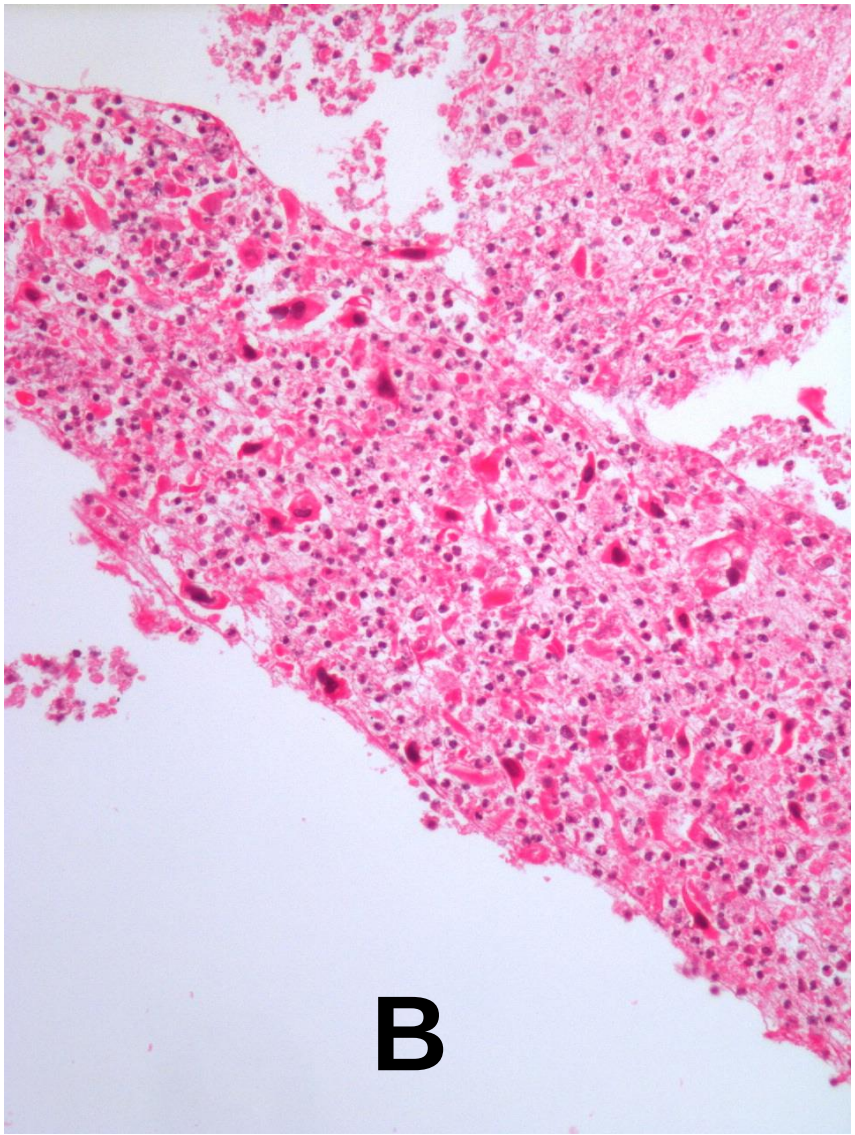
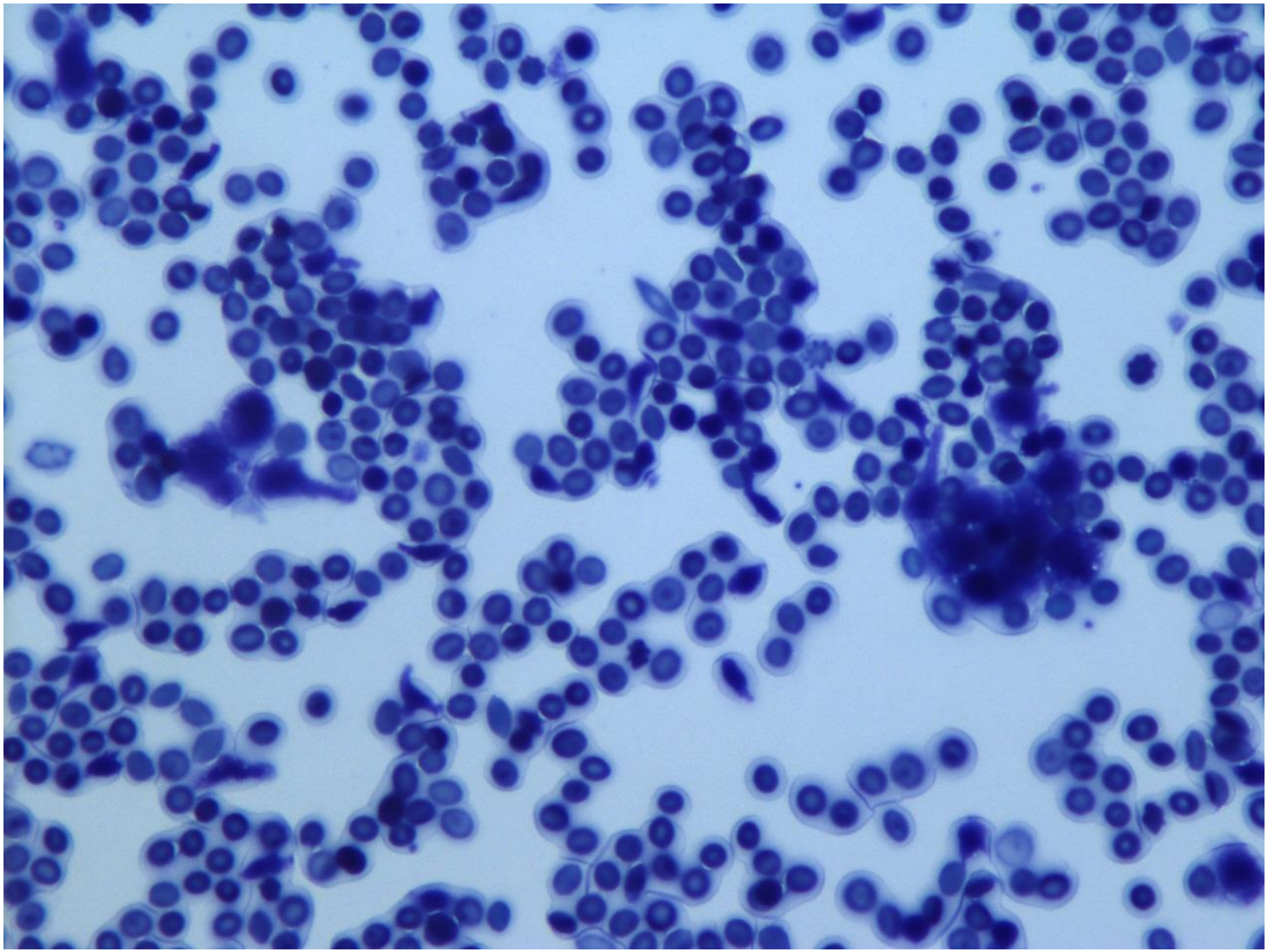


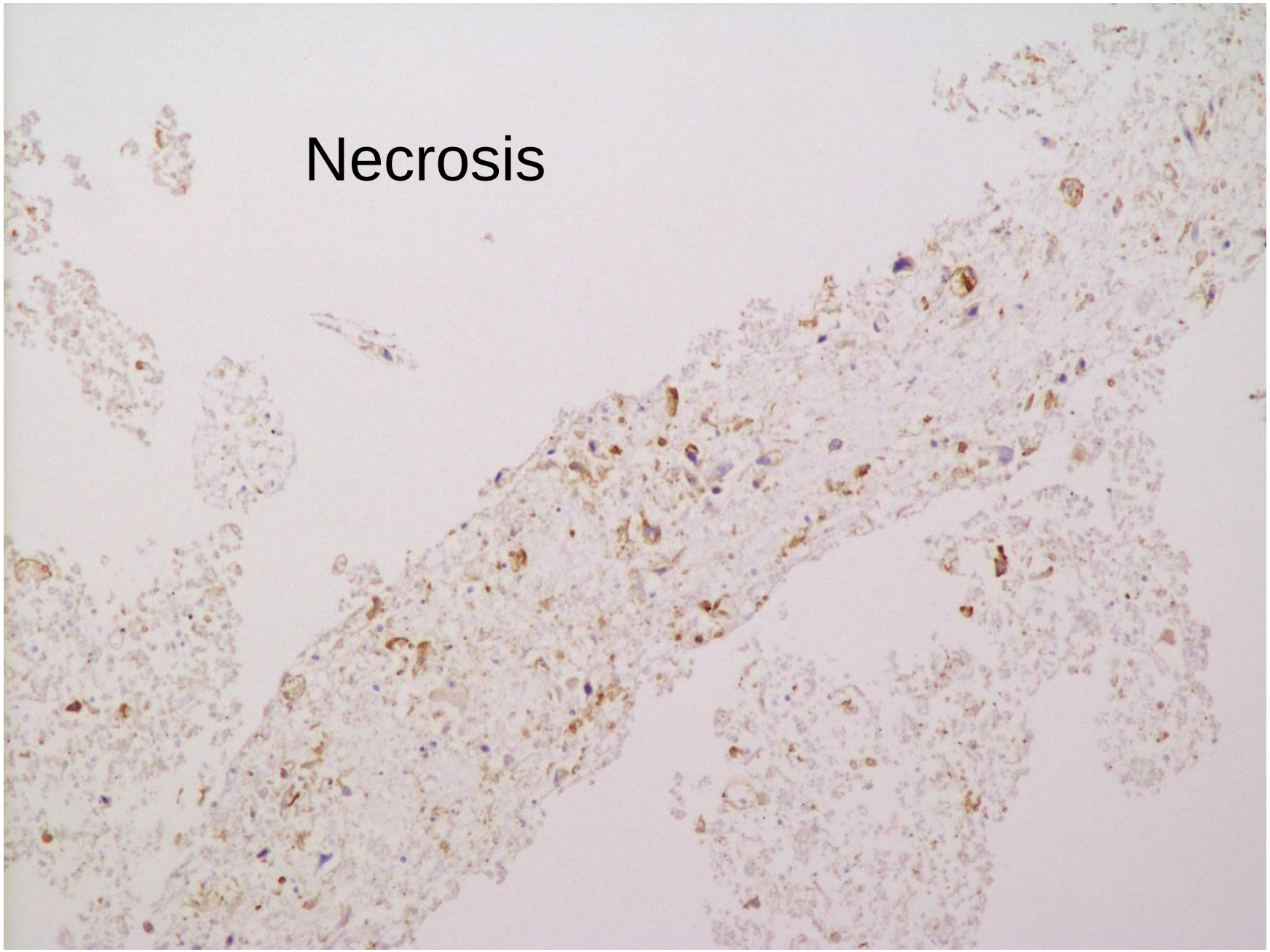


Pleural fluid in formalin



Pre-analytic considerations

- Formalin fixation 6-72 hours
- Necrosis


Necrosis

Pre-analytic considerations

- Formalin fixation 6-72 hours
- Necrosis
- Cellularity >100


H18S04299A
1 HE L1-3
H18M01846B
1 HE L1

Cellular Indequacy for PDL1

- Skov et al Appl Immuno Mol Morph April 2017: 20%
- Sakakibara et al Clinical Lung Cancer Sept 2017: 0.97%
- Heymann et al Cancer cytopathology Dec 2017: 10%

ABM inadequacy

- Insufficient cellularity in 4% cases in 2017
- 3 insufficient for diagnosis and PDL1
- 1 SCC case insufficient cells for PDL1

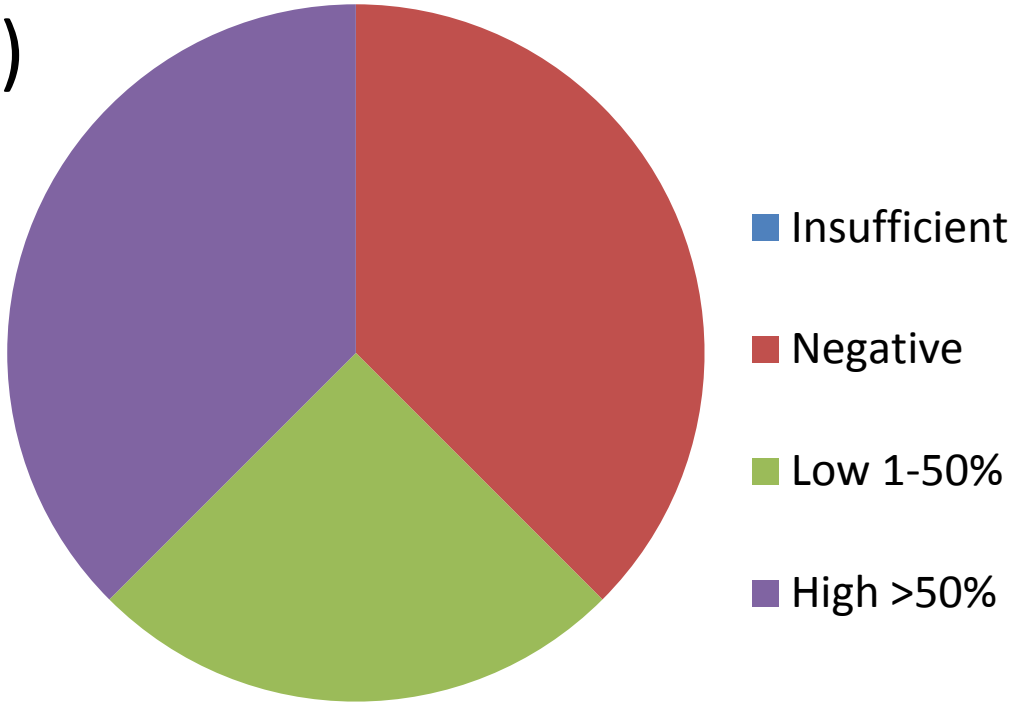
Pre-analytic considerations

- Formalin fixation 6-72 hours
- Necrosis
- Cellularity >100
- Reflex preparation of sections to preserve material

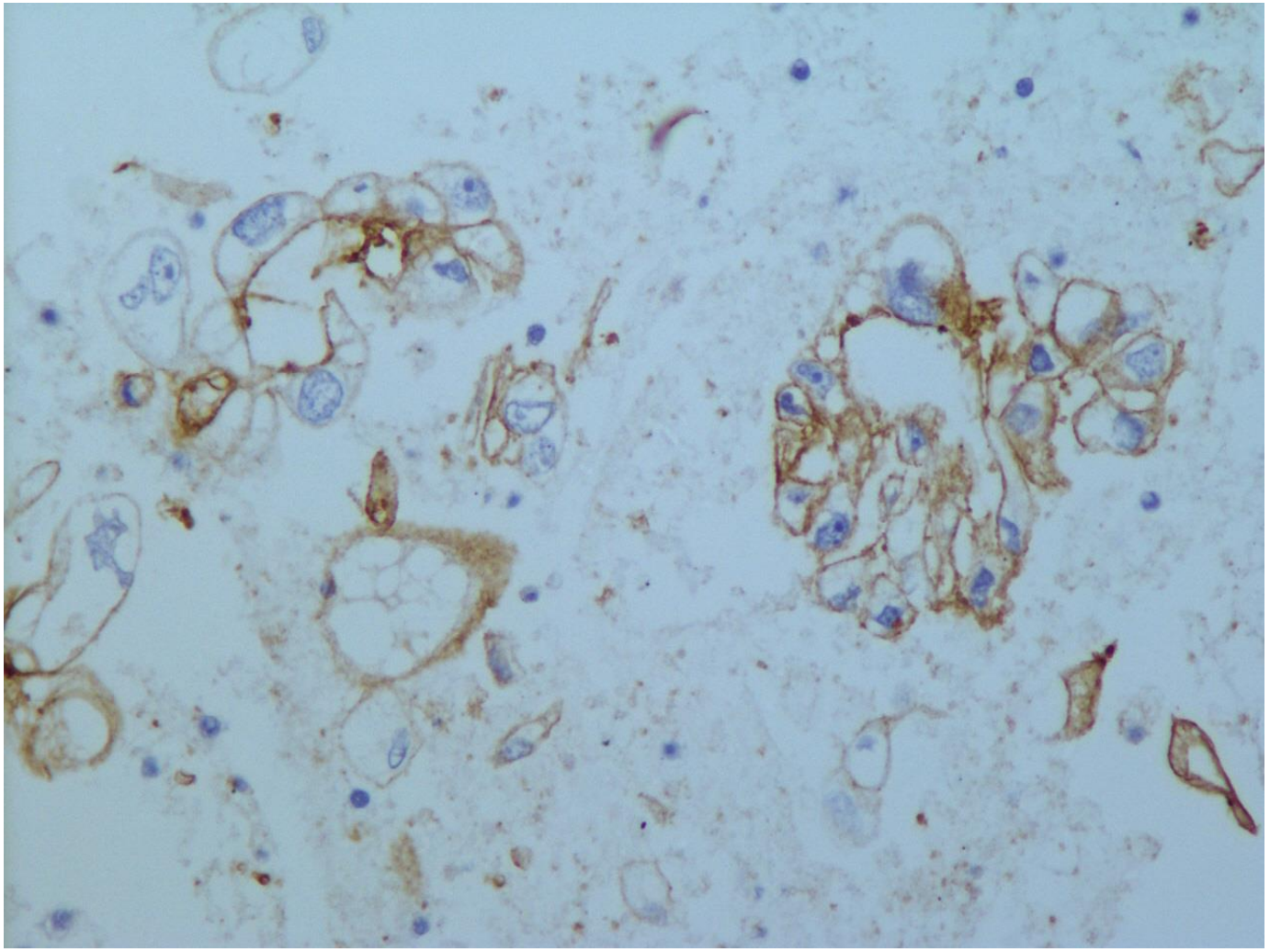
Adenocarcinoma audit: PDL1

- 8/19 requests (42% of adenos tested)
- 3 reported <1%/negative
- 2 as 1-50% (1,3%)
- 3 >50%

(80-90%)



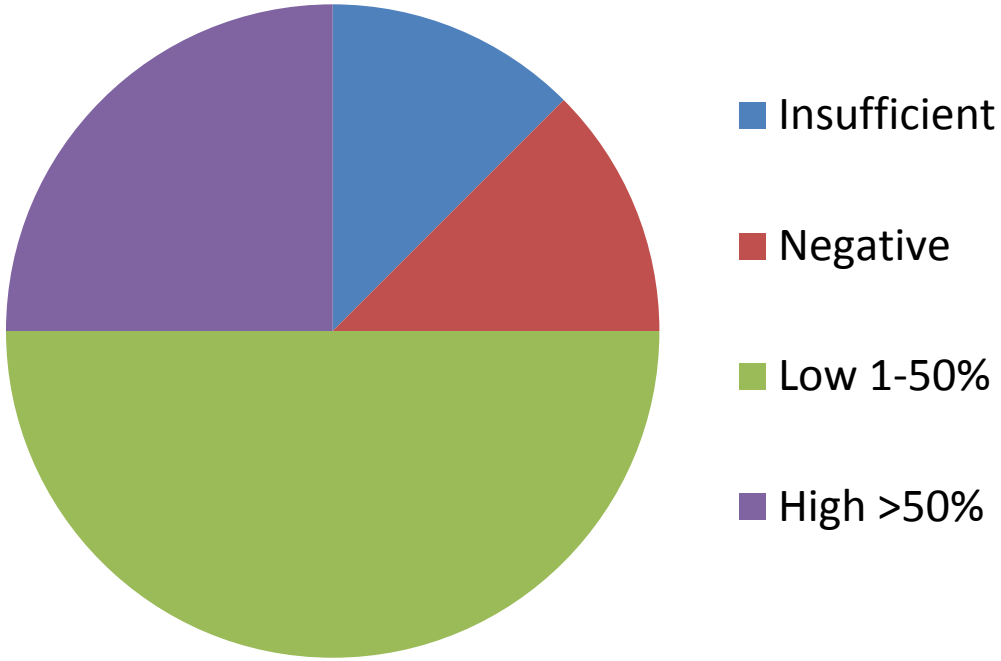
Adenocarcinoma: PDL1 80%



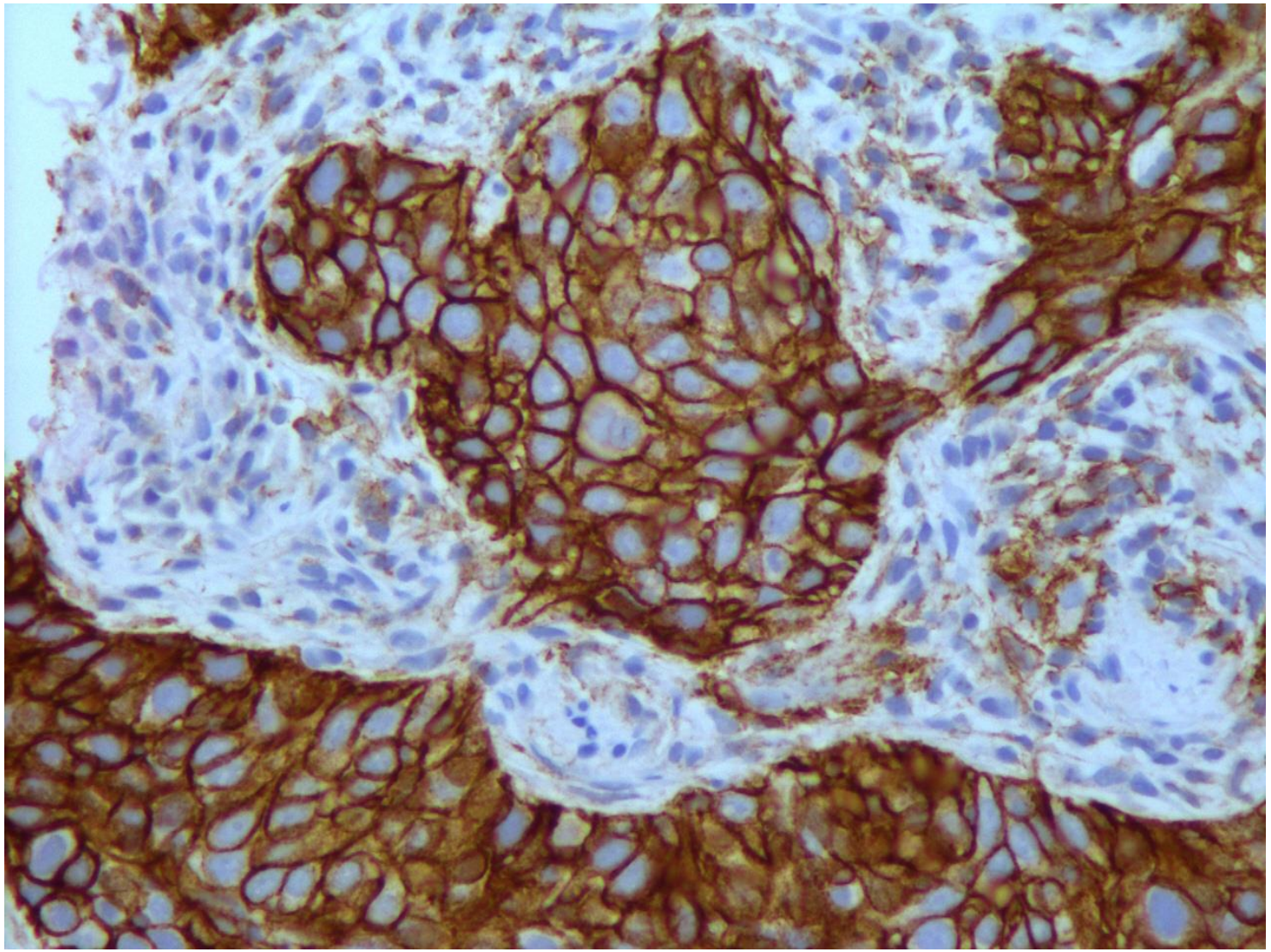
SCC: PDL-1

- 8/14 requests
- 1 insufficient as less than 100 cells
- x1 <1%
- x4 1-50% (2-30%)
- X2 >50%

(80 and 90%)



SCC PDL1



EBUS summary points

- Essential investigation in diagnosis, staging and treatment of lung cancer
- Small amount of tissue for increasing number of tests
- Diagnosis first but p40, TTF1 only
- Formalin 6-72 hours for PDL1 result validity
- Changes require good MDT communication

Further reading

- WHO atlas
- IASLC atlas of PD-L1 Immunohistochemistry testing in Lung Cancer Ed Ming et al 2017 Available on-line @IASLC.org
- Keynote study
- Blueprint study
- Precision molecular Pathology of Lung Cancer Ed Cagle et al 2nd Edition Pub Springer 2018

Acknowledgements

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